REMARKS

I. Request for Continued Examination (RCE)

A Final Action, dated July 26, 2004, was issued in the present application (Application No. 10/027,923). Applicant respectfully submits herewith a Request for Continued Examination (37 C.F.R. 1.114).

II. Status of the Claims

Claims 20-35 and 37-58 were canceled in an Amendment and Response to Restriction Requirement, submitted November 13, 2003. Claims 2-4 and 6-9 were canceled, and claims 1, 5, 10, 15-17, 19 and 36 were amended in the Amendment submitted May 06, 2004. Claims 10-12 have been canceled and claims 1, 5, 13-17, 19 and 36 have been amended in the Amendment submitted herewith. Claims 1, 5, 13-19 and 36 are therefore presently pending in the application.

III. Priority

The Action alleges that priority application, U.S. provisional application No. 60/257,589, filed December 22, 2000, fails to provide adequate support under 35 U.S.C. § 112, first paragraph for claims 1, 5, 10-19 and 36, and as such, the effective filing date of the present application is December 21, 2001. Applicant respectfully traverses.

Applicant reiterates the arguments of record and asserts that both U.S. provisional application No. 60/257,589, filed December 22, 2000 and U.S. application No. 10/027,923, filed December 21, 2001 meet the requirements under 35 U.S.C. § 101 and § 112, first paragraph. Applicant further addresses the rejection of claims 1, 5, 10-19 and 36 under 35 U.S.C. § 101 and § 112, first paragraph below, in Sections IV and V, respectively. Applicant therefore respectfully requests reconsideration of the priority application (U.S. provisional application No. 60/257,589, filed December 22, 2000) as the effective filing date.

IV. Claims Rejected Under 35 U.S.C. § 101

Claims 1-19 and 36 are rejected under 35 U.S.C. § 101, as the claimed invention is allegedly not supported by either a specific and substantial, credible asserted utility or a well established utility. The Action states that the specification fails to exemplify any specific and substantial use of the claimed nucleic acids and/or the encoded protein. Applicant respectfully traverses this rejection.

The claims as presently amended are directed to a protein of SEQ ID NO:2 and nucleic acids encoding the same, wherein the encoded protein forms a dimer with the mGluR5 receptor. The present invention has identified, isolated and characterized, from a human brain derived cDNA library, a full-length open reading frame (SEQ ID NO:1) encoding a protein referred to in the specification as mGluR5M (SEQ ID NO:2). The mGluR5M protein is significantly similar to the N-terminus of the metabotropic glutamate receptor 5 (mGluR5), as detailed in Example 1 of the specification (page 68, line 20 through page 69, line 2). Analysis of mGluR5M mRNA tissue distribution demonstrated that mGluR5M is predominantly expressed in neural tissue (Example 1, page 69, lines 5-36). The mGluR5M protein of the present invention consists of 369 amino acids, wherein amino acids 1-303 are 97% identical to the N-terminal amino acids of human mGluR5 extracellular binding domain (*i.e.*, 1-370 of SEQ ID NO:4). Applicant's data in Table 1 (page 71) demonstrates that the mGluR5M protein forms a dimer with full-length human mGluR5, the biological significance of which is set forth below.

Applicant reiterates the arguments of record and contends that the specification sets forth and supports a specific, substantial and credible utility of the presently claimed invention. More particularly, Applicant has asserted that one specific utility of the invention is the use of the novel mGluR5M protein in assays for identifying compounds (*i.e.*, agonists or antagonists) which modulate mGluR5:mGluR5M dimer activity.

Applicant further asserts that the ability to identify compounds which modulate mGluR5 activity (*e.g.*, antagonize mGluR5 activity) is a substantial and credible utility in the art of neurology and neurological disorders. For example, it was known in the art that antagonists of group I mGluR's (*i.e.*, mGluR1 and mGluR5) are neuroprotective (**Exhibit A**;

Bruno *et al.*, *Neuropharmacology,* 38:199-207, 1999; **Exhibit B**; Schroder *et al.*, *Neuropharmacology*, 38:209-216, 1999) and that the mGluR5 receptor is a therapeutically important target in the areas of pain (**Exhibit C**; Walker *et al.*, *Neuropharmacology*, 40:1-9, 2001; **Exhibit D**; Walker *et al.*, *Neuropharmacology*, 40:10-19, 2001), depression (**Exhibit E**; Tatarczynska *et al, British J. of Pharmacology*, 132:1423-1430, 2001), anxiety (**Exhibit F;** Spooren *et al., J. of Pharm. and Exp. Therapeutics*, 295(3):1267-1275, 2000), Schizophrenia (**Exhibit G**; Brody *et al.*, *Mol. Psychiatry*, 9:35-41, 2004), and various neurodegeneration pathologies such as Huntington's disease, Parkinson's disease, Alzheimer's disease and brain ischemia (**Exhibit H**; Bordi and Ugolini, *Progress in Neurobiology*, 59:55-79, 1999). Applicant therefore asserts that an assay for compounds which modulate the activity of the therapeutic mGluR5 receptor constitutes a substantial, "real world" use and a credible utility. Applicant therefore respectfully requests reconsideration and withdrawal of the rejection of claims 1-19 and 36 under 35 U.S.C. § 101.

The Action further alleges that neither the specification nor art teach the significance of mGluR5:mGluR5M dimerization or the significance of any molecule capable of modulating such interaction. Applicant respectfully traverses this rejection.

Applicant asserts that it was known in the art, at the time the present application was filed, that mGluR5 receptors form non-covalent homodimers which are functionally relevant, and that the site of dimerization (*i.e.*, the N-terminal extracellular domain) is also the domain where glutamate, agonists and antagonists bind mGluR5. For example, it was known in the art that (1) mGluR5 forms homodimers which associate *via* the N-terminal extracellular domain (**Exhibit I**; Romano *et al.*, *J. Biol. Chem.*, 271(45):28612-28616, 1996), (2) glutamate binding resides in this extracellular domain (**Exhibit J**; Takahashi *et al.*, *J. Biol. Chem.*, 268(26):19341-19345, 1993) and (3) competitive agonists and antagonists bind in the N-terminal extracellular domain of mGluR5 (reviewed in **Exhibit K**; Spooren *et al.*, *Trends in Pharmacological Sciences*, 22(7):331-337, 2001). Thus, Applicant asserts there is substantial and credible interest in the art to identify compounds which modulate the activity of group I mGluR receptors.

Furthermore, the significance of group I mGluR dimmers has been reported in the literature and in the present application. For example, Okamoto *et al.* (**Exhibit L**; *J. Biol. Chem., 273*, 13089-13096, 1998) reported the expression of a soluble, extracellular ligand binding domain of mGluR1 and that this domain forms homodimers. It was also demonstrated that there is a cryptic dimer interface of the mGluR1 ligand binding domains, and that each protomer of the dimer can bind a ligand (**Exhibit M**; *Tsuji et al., J. Biol. Chem.*, 275:28144-28151, 2000). Additionally, Kunishima *et al.* (**Exhibit N**; *Nature*, 407:971-977, 2000) crystallized the dimeric ligand binding domain in the presence and absence of glutamate, reporting that the active dimer conformation is stabilized by glutamate binding, and that the rearrangement of the inter-domain and inter-subunit interfaces may be the activation mechanism responsible for extracellular ligand binding. Recent reports in the literature have characterized (a) the mGluR1 dimeric interface, (b) the active versus inactive conformers of the dimer (**Exhibit O**; Tsuchiya *et al., Proc. Natl. Acad. Sci.*, 99:2660-2665, 2002) and (c) the negative cooperativity of glutamate binding in each protomer of the dimer (**Exhibit P**; Suzuki *et al., J. Biol. Chem.*, 279:35526-35534, 2004).

Applicant contends that the newly identified and isolated mGluR5M protein of the present invention, which lacks the C-terminal cytoplasmic (G-protein signaling) domain and transmembrane domains, but retains its N-terminal extracellular ligand binding domain, is a protein endogenously expressed and secreted in the central nervous system (page 69, lines 5-36). The dimerization of the soluble mGluR5M with the membrane bound mGluR5 receptor represents a novel mGluR5 dimer complex, which serves to regulate mGluR5 activity. Applicant therefore asserts that the novel mGluR5M protein of the present has a "specific", "substantial" and "credible" utility in assaying compounds which modulate mGluR5:mGluR5M dimer activity, and as such, respectfully request withdrawal of the rejection of claims 1-19 and 36 are rejected under 35 U.S.C. § 101.

V. Claims Rejected Under 35 U.S.C. § 112, First Paragraph

Claims 1-19 and 36 are rejected under 35 U.S.C. § 112, first paragraph, as the claimed invention is allegedly not supported by either a specific and substantial, credible asserted utility or a well established utility, and as such, a person of skill in the art would not know how to use the claimed invention. Applicants respectfully traverse this rejection.

For the reasons set forth above, Applicant contends that specification asserts at least one substantial and credible utility of the claimed invention, and as such, respectfully request withdrawal of the rejection of claims 1-19 and 36 under 35 U.S.C. § 112, first paragraph.

Claims 5, 10-12, 15-19 and 36 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement. The Action states that "the stringent hybridization conditions are not specified and the DNA insert claimed is not noted to be relevant to plasmid YI176", and has advanced a new rejection with regard to the recitation of "lacking a transmembrane domain". Applicant has amended claim 5, deleting the phrase "lacking a transmembrane domain" and canceled claims 10-13 in the Amendment submitted herewith. Applicant believes that these amendments obviate the rejection, and as such, respectfully request reconsideration and withdrawal of the rejection of claims 5, 10-12, 15-19 and 36 under 35 U.S.C. § 112, first paragraph.

Claims 5, 10-12, 15-19 and 36 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the enablement requirement. The Action states that the claims directed to hybridizing sequences under stringent conditions and sequences that encode a polypeptide lacking a transmembrane domain are not enabled by the specification. As set forth above, Applicant has amended claim 5, deleting the phrase "lacking a transmembrane domain" and canceled claims 10-13 in the Amendment submitted herewith. Applicant believes that these amendments obviate the rejection, and as such, respectfully request reconsideration and withdrawal of the rejection of claims 5, 10-12, 15-19 and 36 under 35 U.S.C. § 112, first paragraph.

VI. Claims Rejected Under 35 U.S.C. § 102(b)

Claim 13 is rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Stratagene random primers, 1991 catalogue, page 66. The Action alleges that "Stratagene teaches the use of random 9-mers capable of hybridizing with all possible gene sequences" and that "As noted in the catalog the primers and included reagents are capable of generation 500-1000 nucleotide segment primers", and as such, the random primers meet the claim limitations because the primers are a complement to SEQ ID NO:1. Applicant has amended claim 13 in the Amendment submitted herewith, deleting the phrase "or a complement thereof". Applicant believes that this amendment obviates the rejection and therefore respectfully request withdrawal of the rejection of claim 13 under 35 U.S.C. § 102(b).

Claims 10-11, 13, 15-19 and 36 are rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Fuller et al. (U.S. Patent 5,981,195). The Action states that "Fuller SEQ ID NO:3 and 4 share 49.7% identity with instant SEQ ID NO:1", Fuller SEQ ID NO:3 shares 24.6% identity with instant SEQ ID NO:1" and Fuller SEQ ID NO:3 also share 40% identity with instant SEQ ID NO:3". The Action alleges that the Fuller sequences would therefore inherently hybridize under stringent conditions to complements of SEQ ID NO:1 and 3. As set forth above, Applicant has amended claim 5, deleting the phrase "lacking a transmembrane domain" and canceled claims 10-13 in the Amendment submitted herewith. Applicant believes that these amendments obviate the rejection, and therefore respectfully request withdrawal of the rejection of claims 10-11, 13, 15-19 and 36 under 35 U.S.C. § 102(b).

If there are any matters which may be resolved or clarified through a telephone interview, the Examiner is requested to contact the undersigned Agent at the number indicated.

The notice set a three-month period to comply, to and including October 26, 2004. Thus, this response is believed to be timely filed. Should any fees be deemed necessary, the Commissioner is authorized to deduct said fees from Deposit Account No. 01-1425.

Respectfully submitted,

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